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14. ABSTRACT

Recent studies have demonstrated preferential accumulation of nanoparticles within tumor. By combining high Z nanoparticles (such as gold) with x-rays from a conventional CT scanner, a significant radiation dose enhancement is possible. In this study, the dose enhancement was quantified based on nanoparticle accumulation within a vessel inside of a phantom. Monte Carlo calculations based on a nanoparticle uptake of 10 mg/g irradiated with 140 kVp x-rays from a CT scanner resulted in a radiation dose enhancement of 2.45. That is, a delivered radiation dose of 10 Gy would be equivalent to delivering 24.5 Gy. The results of this study suggest that this approach holds the potential to deliver a significant dose to the tumor, while limiting the dose to the surrounding normal tissues.

15. SUBJECT TERMS
Nanoparticles, radiation therapy, radiation dose enhancement

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Table of Contents

Introduction

Interest in using nanoparticles for cancer treatment has stemmed from their multiple beneficial properties.[1-5] They are, by definition, small in size and can evade the immune system. Unlabeled nanoparticles have been shown to preferentially accumulate in tumors due to the enhanced permeability and retention effect, stemming from poor tumor vasculature.[6-7] Using this approach, concentrations of nanoparticles in tumor as high as 6.5 mg/g have been demonstrated in mice.[8] In the radiation oncology setting, high atomic number (Z) nanoparticles may provide a local dose enhancement in tumors when combined with low energy x-rays. At energies near the K-shell edges of these materials, the mass energy absorption coefficient (μ_{en}/ρ) may be significantly higher than that of tissue. For materials such as gold, the K-shell edge falls in the energy spectrum of a conventional CT scanner. Irradiating nanoparticles inside tumor with a CT scanner x-ray beam may provide a high dose to the tumor while delivering a reduced dose to surrounding normal tissue. As a first step, a simulation of gold nanoparticles in a phantom can quantify the magnitude of this effect and reveal the best choice of nanoparticle concentration and CT scanner energy for maximizing any dose enhancement. The goal of this study is to characterize the radiation dose enhancement from several different concentrations of gold nanoparticles in a phantom using different CT scanner energies.

Body

The two main tasks from the Statement of Work (SOW) associated with this research are: 1) To design a method to calculate dose to regions of high nanoparticle uptake; and 2) To irradiate a phantom to verify dose calculations. Each will be described below.

Task 1: Design method to calculate dose to regions of high nanoparticle uptake

1a. Designate phantom specifications
1b. Obtain radiation spectrum data for CT scanner
1c. Input beam data into convolution/superposition calculation algorithm
1d. Input beam data into Monte Carlo algorithm
1e. Scan phantom with various concentrations of nanoparticles
1f. Convert CT number data into nanoparticle concentration
1g. Calculate radiation dose enhancement using above algorithms (1c and 1d)

The goal of this study is to calculate the radiation dose enhancement due to high Z nanoparticles irradiated by CT x-ray beams, and then provide experimental verification of the dose calculations. As such, the first part of this study involved designing a phantom that can be used in the experimental verification, and inputting the geometry of this phantom into the dose calculation software so that a direct comparison could be made (SOW 1a). The phantom used for this project was modified based on a previous phantom designed and built in conjunction with Computerized Imaging Reference Systems (CIRS, Norfolk, VA).[9] The phantom is composed of a proprietary water-equivalent plastic and contains an 86 x 66 mm^2 rectangular bore extending half the phantom's length (Figure 1). As the bore extends halfway through the phantom (15 cm), the chosen bore dimensions allow for maximum experimental flexibility. A custom insert was

designed that allows the placement of either an ion chamber or a tube containing the nanoparticles (Figure 2). The ion chamber allows one to obtain absolute dose measurements from the x-ray beam.

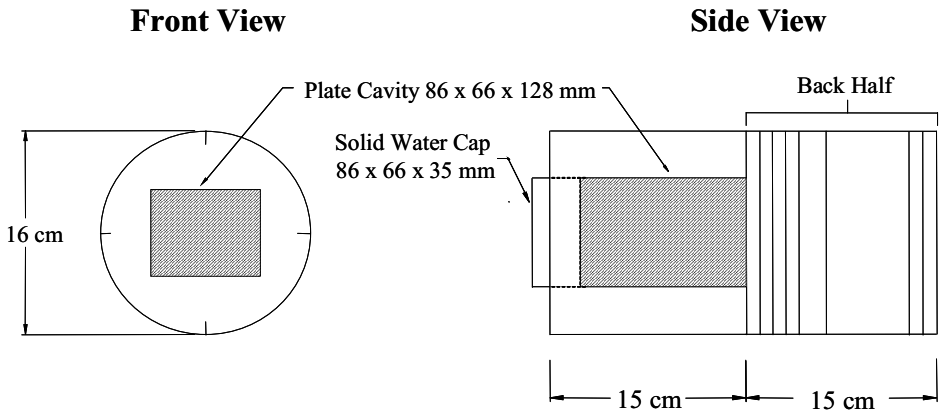

Figure 1: Schematic diagram of the phantom. The phantom consists of a cylinder with a 16 cm diameter. As shown on the front and side views, the plate cavity is modified to include an insert for the ion chamber/vessel.

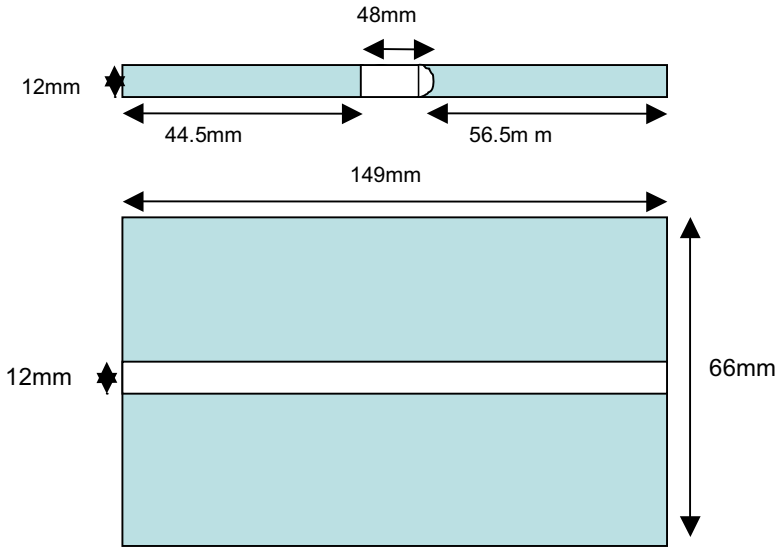

Figure 2: Schematic diagram of the phantom insert. The top diagram shows the insert modified to accommodate the nanoparticle vessel. A separate insert (not shown) was designed for the ion chamber.

Based on the phantom design as described above, a digital version of the phantom was created and used as the input geometry for dose calculations within the Monte Carlo N-Particle eXtended (MCNPX) program. MCNPX is a generalized Monte Carlo code that simulates the transport and interaction of radiation with matter. The program was obtained from the Radiation Safety Information Computational Center (RSICC) in Oak Ridge, TN. All simulations were

performed using MCNPX version 2.6.0 on a Windows based PC. Photon interaction cross sections were drawn from the default MC-PLIB04 tables, which are based on the ENDF/B-VI, Release 8 nuclear data files. Electron interaction data is taken from the RSICC-EL03 library.

The tumor volume was simulated as a small cavity containing water within the phantom (Figure 3). Various concentrations of gold nanoparticles were simulated inside the tumor: no gold, 1mg/g, 5 mg/g and 10 mg/g (SOW 1e-f). These concentrations were based upon in vivo studies performed in mice.[10] Additionally, higher concentrations of gold nanoparticles (25 mg/g, 50 mg/g and 100 mg/g) were also considered as these represent theoretical uptakes that may occur with a highly targeted system. The radiation sources used in this study consist of diagnostic x-ray spectra from 50, 80, 100 and 140 kVp x-rays which are consistent with those produced by conventional CT scanners (SOW 1b).[11,12]

The energy spectra were input into MCNPX for radiation energy deposition calculations (SOW 1c-d). An example of the program developed to perform the dose calculations is shown within the appendix. Because the programming language used within MCNPX is Fortran-based, it is very much dependent on syntax. As such this portion of the research took longer than expected as significant time was required to learn the intricacies of the MCNPX programming language.

All possible combinations of x-ray energy and nanoparticle concentration were considered. For each, the spectrum of energy deposited was tallied within the tumor volume as well as regions outside the tumor (simulating normal tissue). Each scenario was run using 10^9 photons, ensuring that the relative uncertainty in the MCNP tally was less than 5%, and that other statistical checks had passed. Histories were cut off at a low energy threshold of 1 keV. These metrics are commonly used benchmarks in MCNP simulations that help to ensure accurate results.

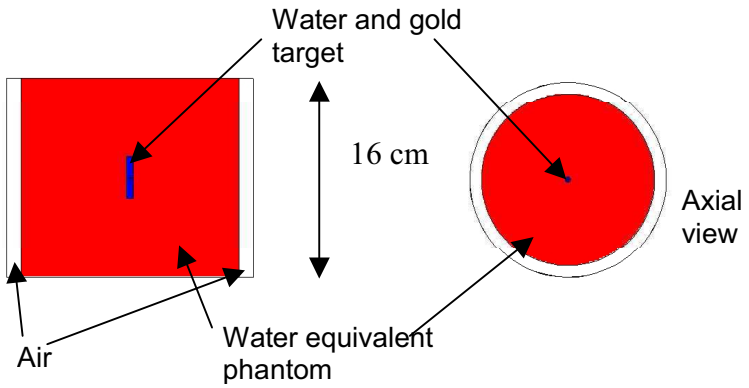

Figure 3: Geometry of the phantom and tumor as input into MCNPX. The simulated tumor (shown in blue) consists of a small vial containing water. The concentration of gold nanoparticles within this vial is varied based on experimental and hypothetical values of gold nanoparticle uptake.

Results for dose enhancement were determined using the energy pulse height F8 tally within MCNPX, taken in the simulated tumor region (SOW 1g). Tallies were binned into 5 keV bins up to 140 keV. The ratio of the total energy deposited for various concentrations of nanoparticles, relative to no nanoparticles, was taken as the measure of the radiation dose enhancement due to the nanoparticles. Figure 4 shows the spectrum of relative energy deposited within tumor versus x-ray beam energy. As can be seen from these plots, the relative amount of energy deposited in the volume increases as the gold nanoparticle concentration increases. This increase in energy is due to the higher cross section of gold relative to water/tissue. Integration over this spectrum can be used to determine the relative dose enhancement (with respect to no nanoparticles). As shown in the table below, significant dose enhancement is observed. For the case of a 10 mg/g nanoparticle concentration, the relative dose enhancement is 2.45. That is, a delivered dose of 10 Gy would be equivalent to delivering 24.5 Gy, illustrating the potential of this approach.

The radiation dose enhancement for a concentration of 10 mg/g of gold nanoparticle is also plotted as a function of the nanoparticle concentration as shown in Figure 5. Note that the dose enhancement is nonlinear. Increasing the nanoparticle concentration by a factor of 10 (10 mg/g to 100 mg/g) increases the dose enhancement factor by approximately 5. This nonlinearity is due to self-absorption of the x-rays within the high Z nanoparticle material. The results of this research are similar to a previous study on the subject. Cho et al. simulated a nanoparticle concentration of 7 mg/g irradiated with 140 kVp x-rays.[11] Using the EGS4 Monte Carlo code, they observed a relative dose enhancement of 2.11. Using our approach, a relative dose enhancement of 2.06 is calculated. These results are very consistent (agreement < 2.5%) given the differences in geometry and the limitations of the calculations themselves.

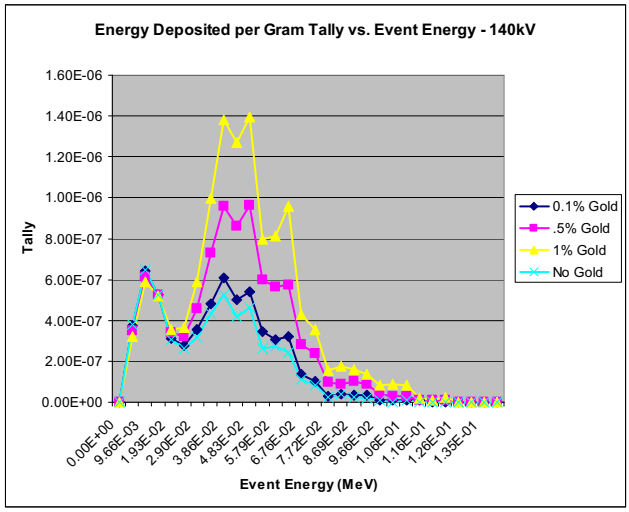

Figure 4: Spectrum of the energy deposited within the simulated tumor for 140 kVp x-rays irradiating the phantom having various concentrations of gold nanoparticles (see figure legend). As the nanoparticle concentration increases, the amount of energy deposited increases due to the higher cross-section of the gold (relative to water) at these energies.

Nanoparticle Concentration	Relative Dose Enhancement
0mg/g	1.00
1mg/g	1.16
5mg/g	1.80
10mg/g	2.45

Table 1: Radiation dose enhancement as a function of nanoparticle concentration within the tumor. The results were obtained by integration of the spectrum shown in Figure 4, taking the ratio of the nanoparticles relative to no nanoparticles.

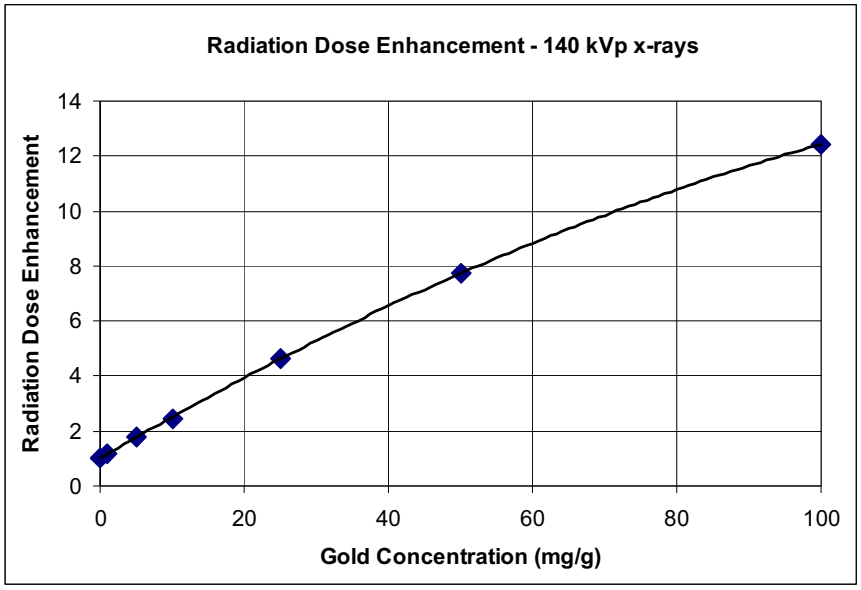

Figure 5: The radiation dose enhancement as a function of the nanoparticle concentration for 140 kVp x-rays. Note that the dose enhancement factor does not increase linearly due to self absorptions of the x-rays within the high Z materials in the tumor.

In addition to the Monte Carlo calculations showing dose enhancement in the tumor region, an examination of the dose deposited in the remainder of the phantom was also made. The purpose of these studies was to determine if any dose enhancement extended beyond the material containing gold nanoparticles. The results of this analysis reveal no dose enhancement throughout the majority of the phantom. However, a small decrease in the energy deposited was noted in the region just outside of the tumor. This effect is due to a "shadowing" caused by the significant attenuation of the high Z nanoparticle material. Beyond this immediate region, the dose from scattered x-rays "fills in" this shadow region such that the dose decrease disappears. This effect was unanticipated and is currently being further investigated.

Task 2: Irradiate phantom to verify dose calculations

2a. Create treatment plan using multiple non-coplanar angles
2b. Verify deliverability of plan on CT scanner
2c. Calibrate dosimeters (TLDs) in phantom material
2d. Deliver dose distribution to phantom with TLDs in place
2e. Analyze measurements; compare with calculations

The results of these simulations of a phantom with different concentrations of gold nanoparticles irradiated by an x-ray source reveal a dose enhancement relative to no nanoparticle presence. Dose enhancements of 2.45 times for nanoparticle concentrations of up to 10 mg/g indicate that localizing nanoparticles in tumor may be effective at providing an improved therapeutic ratio. The results of this simulation are used to guide measurements for confirmation of this effect. These measurements examine dose enhancement in the nanoparticle region, as well as investigate the nature of any dose decrease in the area immediately surrounding the nanoparticle region.

As spatial precision is key to performing these types of experiments, accurate, reproducible placement of the phantom is imperative. To that end, a series of six external guide markers are used to align the phantom. Three guide markers apiece exist at two axial positions on the phantom. Two guide markers (one in each axial group) are at the phantom apex, directly above the midline of the anterior wall of the phantom bore. Similarly, two markers are located directly to the right or left of the midline of the corresponding bore wall. By aligning the guide markers to the laser positioning system, the phantom can be reproducibly placed at the same point relative to the CT scanner (SOW 2b). To prevent movement during scanning and treatment, the phantom is placed on a plastic stand. The stand is a single molded sheet of 0.15 cm thick plastic. It has a 27.8 x 12.2 cm base with the top molded to the curvature of the phantom. When in the stand, the lowest point of the phantom is 1.2 cm above the surface it resides on.

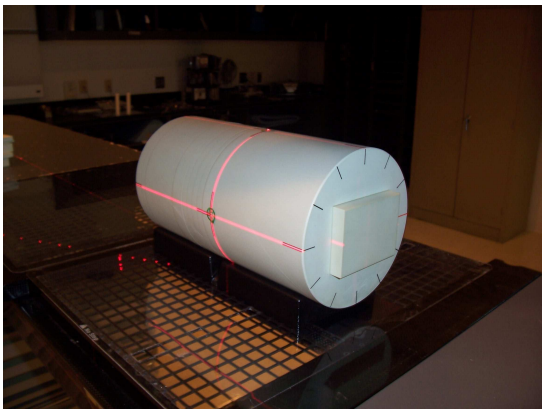

Figure 7: Photo of the phantom illustrating the guide markers and laser system used for precise placement on the CT scanner.

The experimental portion of this study is currently underway, and we have requested a "no cost extension" to complete the measurements and analyze the data. We expect to complete this portion of the project within the next few months. Briefly, a treatment plan was designed to deliver an enhanced dose to the tumor region within the phantom (SOW 2a). Next, small thermoluminescent dosimeters (TLDs) are placed within the tumor cavity. The TLDs are irradiated both with and without nanoparticles in the cavity (SOW 2c-d). The ratio of the energy deposited within these TLDs is used to experimentally verify the radiation dose enhancement provided by the nanoparticles (SOW 2e).

Key Research Accomplishments

Designed phantom to experimentally verify radiation dose enhancement calculations.

Implemented code to calculate radiation dose enhancement based on tumor uptake of gold nanoparticles using the previously designed phantom.

Observed diagnostic x-ray beams can be used to provide radiation dose enhancement with higher energy diagnostic x-rays achieving a higher degree of dose enhancement relative to lower energies.

Radiation dose enhancement factors as high as 2.45 were calculated for nanoparticle concentrations of 10 mg/g – comparable to concentrations observed *in vivo*.

Observed a reduced dose outside the tumor volume (normal tissue dose reduction) due to "shadowing" from the high-density nanoparticle materials.

Initiated experiments to confirm calculated dose.

Reportable Outcomes

Matthew Quinn, PhD, presented this research at the Young Investigator's Symposium of the Midwest Chapter of the American Association of Physicists in Medicine (AAPM), April 2010.

Abstract presented at the Annual Meeting of the American Association of Physicists in Medicine (AAPM), July 2010.

Matt Quinn, PhD, post-doctoral fellow on this project, applied for and received a position at Fermi National Laboratory based on expertise developed in using the MCNP code for this project.

Conclusion

In summary, we have quantified the radiation dose enhancement due to the irradiation of gold nanoparticles with the x-rays from a conventional CT scanner. At the current levels of nanoparticle uptake by tumor, the use of 140 kVp x-rays from a typical CT scanner will provide a radiation dose enhancement of 2.45. That is, a delivered dose of 10 Gy would be equivalent to delivering 24.5 Gy to the tumor. Such an approach may provide a significant therapeutic ratio improving the potential to deliver tumorcidal doses while minimizing the dose deposited (and potential complications) in normal tissues.

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Appendix

Sample Code Used for Simulations

```
$ Volumes of interest definitions
1   264  -8  17 -9 -16 10 -5 8  $Source surround material
2   264  -8 3 -17 6 -5 -9 10  $Source surround material
3   264  -8 16 -4 6 -5 -9 10  $Source surround material
4    0        19
5   264  -8  21 -20 -22 23 -24 25 $Plate used for check
6   1 -0.997 -26 -27 28 #7 #8 #10
7   5 -0.997 -29 -31 32 $ detector 1
8   1 -0.997 -30 -31 32 $ radial detector 2
9   204 -0.001225 -19 #1 #2 #3 #5 #6 #7 #8 #10  $Volume encompassing problem
10   1 -0.997 -33 -31 32 $ radial detector

$ Surface definitions
1       px 7.5
2       px -7.5
3       px -7.0
4       px 7.0
5       py 45.0
6       py 35.10
7       py 38.0
8       py 41.5
9       pz 4.5
10      pz -4.5
11      pz 5.0
12      pz -5.0
13      pz 2.0
14      pz 1.5
15      px 2.0
16      px 0.15
17      px -0.15
18      px -2.0
19      so 50
20      pz 6
21      pz -6
22      px 20
23      px -20
24      py -20
25      py -25
26 Cx 7.9375 $ cylinder
27 Px 7.30 $ upper surface of cylinder
28 Px -7.30 $ lower surface of cylinder
```

```
  29 Cx 2.0 $ centerline detector
  30 C/x -6.5 0. 0.5 $ radial detector
  31 Px 1.5 $ upper surface of middle slice
  32 Px -1.5 $ lower surface of middle slice
  33 C/x -4.5 0. 0.5 $ radial detector

$Material Definitions
m1 1001 -0.111915 &
   8016 -0.888085
m5 1001 -0.111915 &
   8016 -0.888085 &
  79000  -0.00100000
m264  6000.60c        -0.0003  $SS-304,SS-304L (with ENDF-VI)
     14000.60c        -0.005 15031.60c     -0.000225 16000.60c      -0.00015
     24050.60c      -0.00793 24052.60c     -0.159031 24053.60c     -0.018378
     24054.60c     -0.004661 25055.60c         -0.01 26054.60c     -0.039996
     26056.60c     -0.644764 26057.60c     -0.015026 26058.60c     -0.002039
     28058.60c      -0.06234 28060.60c     -0.024654 28061.60c     -0.001085
     28062.60c     -0.003504 28064.60c     -0.000917
m204  7014.60c      -0.755636  $air (US S. Atm at sea level)
     8016.60c      -0.231475 18000.59c     -0.012889
$Physics parameter definitions
mode  p e
phys:p 0.17
imp:p  1 1 1 0 1 1 1 1 1 1
imp:e  1 1 1 0 1 1 1 1 1 1
SDEF par=2  ERG=d3 POS= 0 40 0  VEC=0 -1 0 DIR=d1
SI1 h -1 0.14 0.85 0.95 1
SP1 d 0 0.0 0 0 1
$CT spectrum definitions
SI3 L 0.014 &
0.016 &
0.018 &
0.02 &
0.022 &
0.024 &
0.026 &
0.028 &
0.03 &
0.032 &
0.034 &
0.036 &
0.038 &
0.04 &
0.042 &
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0.136 &
0.138 &
0.14
SP3 0.06 &
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2.12 &
5.18 &
9.54 &
14.56 &
19.53 &
23.88 &
27.30 &
29.76 &
31.31 &
32.09 &
32.27 &
31.97 &
31.33 &
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19.27 &
35.52 &
21.96 &
13.74 &
13.01 &
12.55 &
12.09 &
11.62 &
11.17 &
10.72 &
10.27 &
9.82 &
9.39 &
8.96 &
8.53 &
8.12 &

7.71 &
7.30 &
6.90 &
6.50 &
6.11 &
5.72 &
5.35 &
4.99 &
4.62 &
4.25 &
3.90 &
3.54 &
3.19 &
2.84 &
2.50 &
2.17 &
1.84 &
1.50 &
1.18 &
0.86 &
0.54 &
0.23 &
0.00
$Output definitions
F8:P,e 7 $ pulse height in center
E8 0.0 28I 0.14 $ Pulse height tally with 5 keV interval
nps 1000000000

Abstract Presentation

M Quinn, M Gao, K Albuquerque, J Roeske. Monte carlo simulation of dose enhancement in tumors using gold nanoparticles. Presented at 52nd Annual Meeting of the American Association of Physicists in Medicine, July 2010.

Purpose:
In the radiation oncology setting, high atomic number (Z) nanoparticles may provide a local dose enhancement in tumors when combined with low energy x-rays. At energies near the K-shell edges of these materials, the mass energy absorption coefficient (μ_{en}/ρ) may be significantly higher than that of tissue. For materials such as gold, the K-shell edge falls in the lower energy spectrum of a conventional CT scanner. Irradiating nanoparticles inside tumor with a CT scanner may provide a high dose to the tumor while sparing healthy surrounding tissue. As a first step, a simulation of gold nanoparticles in a phantom can quantify the magnitude of this effect.

Methods:
Monte Carlo simulations were performed for different concentrations of gold using the program MCNPX. Simulations were performed using a cylindrical phantom with a tumor having various concentrations of gold nanoparticles. Four concentrations of nanoparticles were used: no gold, 1mg/g, 5mg/g, 10mg/g. The source of radiation was modeled using the spectrum of a 140kVP CT scanner. Each scenario was run using 10^9particles.

Results:
For all cases, the total energy deposited in the target was determined. These calculations indicate that using nanoparticles provides a sizeable increase in the energy deposited inside the target. For 1mg/g, 5mg/g, and 10mg/g nanoparticle concentration, the dose increases were 1.13, 1.78, and 2.58 times relative to no gold.

Conclusions:
Monte Carlo simulations of a phantom with different concentrations of gold nanoparticles irradiated by an x-ray source reveal a significant dose enhancement relative to no nanoparticle presence. Dose enhancements of over 2.5 times for nanoparticle concentrations of up to 10mg/g indicate that localizing nanoparticles in tumor may be effective at providing an improved therapeutic ratio. The results of this simulation can be used to guide measurements for confirmation of this effect.

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